

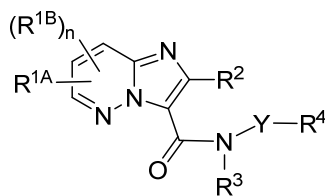
such as hallucinations, insomnia, nausea, and constipation. Further, patients often develop tolerance to these drugs such that the drugs become ineffective at treating the symptoms of the disease, while sometimes also producing a movement disorder side effect called dyskinesia. Diffuse Lewy Body disease is a dementia that is sometimes confused with Alzheimer's disease.

- 5 **[0005]** Accordingly, the need exists for new therapeutic agents for treating Gaucher disease, Parkinson's disease, and related medical disorders. The present invention addresses this need and provides other related advantages.

SUMMARY

- [0006]** The present disclosure provides substituted imidazo[1,2-*b*]pyridazine compounds,
 10 substituted imidazo[1,5-*b*]pyridazine compounds, related compounds, compositions containing such compounds, medical kits, and methods for using such compounds and compositions to treat medical disorders, *e.g.*, Gaucher disease, Parkinson's disease, Lewy body disease, dementia, multiple system atrophy, epilepsy, bipolar disorder, schizophrenia, an anxiety disorder, major depression, polycystic kidney disease, type 2 diabetes, open angle glaucoma,
 15 multiple sclerosis, endometriosis, and multiple myeloma, in a patient. Various examples of the present disclosure are described in further detail below.

[0006a] In one aspect of the present disclosure, there is provided a compound of Formula I:



(I)

20

or a pharmaceutically acceptable salt thereof, wherein:

R^{1A} is 6-membered aryl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_3 - C_6 cycloalkyl, and cyano;

2a

R^{1B} is C₁-C₆ alkyl;

R² is hydrogen;

R³ is hydrogen;

R⁴ is one of the following:

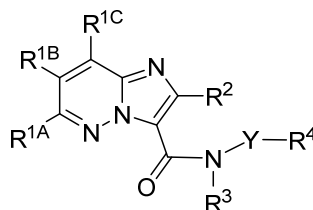
- 5
- C₃-C₈ cycloalkyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C₁-C₆ alkyl, halogen, C₁-C₆ haloalkyl, C₃-C₆ cycloalkyl, hydroxyl, C₁-C₆ alkoxy, C₂-C₄ alkynyl, and -(C₂-C₄ alkynyl)-C₁-C₆ alkoxy; or

- C₁₋₆ alkyl;

10 Y is C₁-C₆ haloalkylene or C₁-C₆ alkylene; and

n is 1.

[0006b] In another aspect of the present disclosure, there is provided a compound of Formula I-B:



(I-B)

or a pharmaceutically acceptable salt thereof, wherein:

R^{1A} is 6-membered aryl substituted with 1 or 2 substituents independently selected from fluorine and cyano;

20 R^{1B} and R² are hydrogen;

R^{1C} is C₁-C₆ alkyl;

R³ is hydrogen;

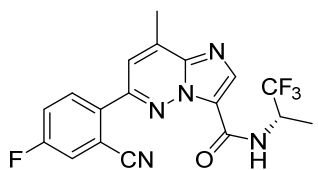
R⁴ is (i) C₃-C₈ cycloalkyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C₁-C₈ alkyl, C₁-C₆ haloalkyl, and C₁-C₆ alkoxy, or (ii) C₁-

25 C₆ alkyl; and

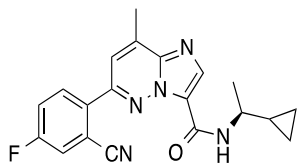
2b

Y is C₁-C₆ alkylene or C₁-C₆ haloalkylene.

[0006c] In a further aspect of the present disclosure, there is provided a compound having the following formula or a pharmaceutically acceptable salt thereof:



5 **[0006d]** In another aspect of the present disclosure, there is provided a compound having the following formula or a pharmaceutically acceptable salt thereof:

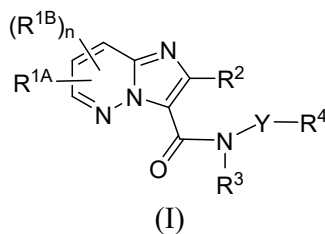


[0006e] In a further aspect of the present disclosure, there is provided a pharmaceutical composition, comprising a compound disclosed herein and a pharmaceutically acceptable carrier.

[0006f] In another aspect of the present disclosure, there is provided a compound disclosed herein for use in treating a disorder selected from the group consisting of Gaucher disease, Parkinson's disease, Lewy body disease, dementia, multiple system atrophy, epilepsy, bipolar disorder, schizophrenia, an anxiety disorder, major depression, polycystic kidney disease, type 2 diabetes, open angle glaucoma, multiple sclerosis, endometriosis, and multiple myeloma.

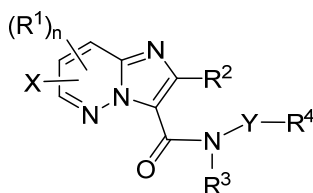
[0006g] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein in the manufacture of a medicament for treating a disorder selected from the group consisting of Gaucher disease, Parkinson's disease, Lewy body disease, dementia, multiple system atrophy, epilepsy, bipolar disorder, schizophrenia, an anxiety disorder, major depression, polycystic kidney disease, type 2 diabetes, open angle glaucoma, multiple sclerosis, endometriosis, and multiple myeloma.

[0007] The present disclosure also provides a family of substituted imidazo[1,2-*b*]pyridazine compounds embraced by Formula I that may be used in the methods, compositions, and kits described herein, wherein Formula I is represented by:



or a pharmaceutically acceptable salt thereof, wherein the variables are as defined in the detailed description.

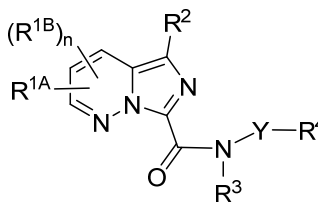
[0008] The present disclosure also provides a family of substituted imidazo[1,2-*b*]pyridazine compounds embraced by Formula II that may be used in the methods, compositions, and kits described herein, wherein Formula II is represented by:



(II)

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined in the detailed description.

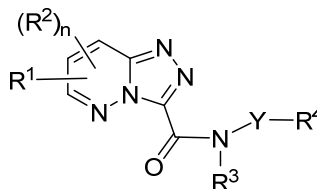
- 5 **[0009]** The present disclosure also provides a family of substituted imidazo[1,5-*b*]pyridazine compounds embraced by Formula III that may be used in the methods, compositions, and kits described herein, wherein Formula III is represented by:



(III)

- 10 or a pharmaceutically acceptable salt thereof, wherein the variables are as defined in the detailed description.

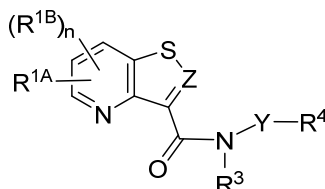
[0010] The present disclosure also provides a family of compounds embraced by Formula IV that may be used in the methods, compositions, and kits described herein, wherein Formula IV is represented by:



(IV)

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined in the detailed description.

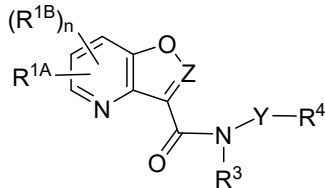
[0011] The present disclosure also provides a family of compounds embraced by Formula V that may be used in the methods, compositions, and kits described herein, wherein Formula V is represented by:



(V)

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined in the detailed description.

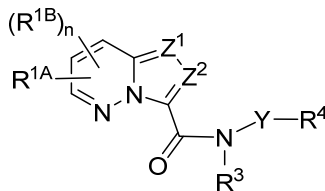
[0012] The present disclosure also provides a family of compounds embraced by Formula VI that may be used in the methods, compositions, and kits described herein, wherein Formula VI is represented by:



(VI)

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined in the detailed description.

[0013] The present disclosure also provides a family of compounds embraced by Formula VII that may be used in the methods, compositions, and kits described herein, wherein Formula VII is represented by:



(VII)

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined in the detailed description.

[0014] The present disclosure also provides a pharmaceutical composition, comprising a pharmaceutically acceptable carrier and a substituted imidazo[1,2-*b*]pyridazine compound, substituted imidazo[1,5-*b*]pyridazine compound, or related compound described herein, such as a compound of Formula I, II, III, IV, V, VI, or VII. In certain examples, the present disclosure also provides a pharmaceutical composition, comprising a pharmaceutically acceptable carrier and a substituted imidazo[1,2-*b*]pyridazine compound described herein, such as a compound of Formula I or II. In certain other examples, the present disclosure also provides a pharmaceutical composition, comprising a pharmaceutically acceptable carrier and a substituted imidazo[1,5-*b*]pyridazine compound described herein, such as a compound of Formula III.

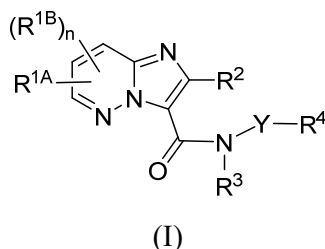
[0015] The present disclosure also provides a method of treating a disorder, e.g., Gaucher disease, Parkinson's disease, Lewy body disease, dementia, multiple system atrophy, epilepsy, bipolar disorder, schizophrenia, an anxiety disorder, major depression, polycystic kidney disease, type 2 diabetes, open angle glaucoma, multiple sclerosis, endometriosis, and multiple myeloma, in a patient. The method comprises administering to a patient in need thereof a therapeutically effective amount of a substituted imidazo[1,2-*b*]pyridazine compound, substituted imidazo[1,5-*b*]pyridazine compound, or related compound described herein, such as a compound of Formula I, II, III, IV, V, VI, or VII, to treat the disorder, e.g., Gaucher disease, Parkinson's disease, Lewy body disease, dementia, multiple system atrophy, epilepsy, bipolar disorder, schizophrenia, an anxiety disorder, major depression, polycystic kidney disease, type 2 diabetes, open angle glaucoma, multiple sclerosis, endometriosis, or multiple myeloma.

DETAILED DESCRIPTION

[0016] The invention provides substituted imidazo[1,2-*b*]pyridazine compounds, substituted imidazo[1,5-*b*]pyridazine compounds, related compounds, compositions containing such compounds, medical kits, and methods for using such compounds and compositions to treat medical disorders in a patient. The practice of the present invention employs, unless otherwise indicated, conventional techniques of organic chemistry, pharmacology, cell biology, and biochemistry. Such techniques are explained in the literature, such as in "Comprehensive Organic Synthesis" (B.M. Trost & I. Fleming, eds., 1991-1992); "Current protocols in

What is claimed is:

1. A compound of Formula I:



or a pharmaceutically acceptable salt thereof, wherein:

R^{1A} is 6-membered aryl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_3 - C_6 cycloalkyl, and cyano;

R^{1B} is C_1 - C_6 alkyl;

R^2 is hydrogen;

R^3 is hydrogen;

R^4 is one of the following:

- C_3 - C_8 cycloalkyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1 - C_6 alkyl, halogen, C_1 - C_6 haloalkyl, C_3 - C_6 cycloalkyl, hydroxyl, C_1 - C_6 alkoxy, C_2 - C_4 alkynyl, and $-(C_2$ - C_4 alkynyl)- C_1 - C_6 alkoxy; or
- C_1 - C_6 alkyl;

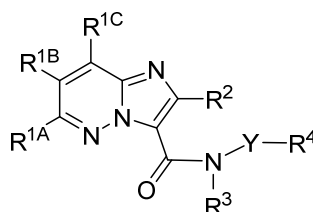
Y is C_1 - C_6 haloalkylene or C_1 - C_6 alkylene; and

n is 1.

2. The compound of claim 1, wherein Y is C_1 - C_6 alkylene.
3. The compound of claim 1, wherein Y is C_1 - C_6 haloalkylene.
4. The compound of claim 2, wherein R^4 is C_3 - C_8 cycloalkyl.
5. The compound of claim 3, wherein R^4 is C_1 - C_6 alkyl.
6. The compound of claim 1, wherein R^{1A} is attached at the 6-position of the imidazo[1,2-b]pyridazinyl.
7. The compound of claim 4, wherein R^{1A} is attached at the 6-position of the imidazo[1,2-b]pyridazinyl.

8. The compound of claim 5, wherein R^{1A} is attached at the 6-position of the imidazo[1,2-b]pyridazinyl.

9. A compound of Formula I-B:



(I-B)

or a pharmaceutically acceptable salt thereof, wherein:

R^{1A} is 6-membered aryl substituted with 1 or 2 substituents independently selected from fluorine and cyano;

R^{1B} and R^2 are hydrogen;

R^{1C} is C_1 - C_6 alkyl;

R^3 is hydrogen;

R^4 is (i) C_3 - C_8 cycloalkyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_1 - C_8 alkyl, C_1 - C_6 haloalkyl, and C_1 - C_6 alkoxy, or (ii) C_1 - C_6 alkyl; and

Y is C_1 - C_6 alkylene or C_1 - C_6 haloalkylene.

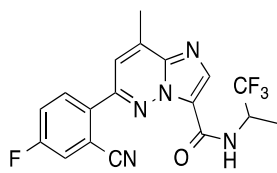
10. The compound of claim 9, wherein Y is C_1 - C_6 alkylene.

11. The compound of claim 9, wherein Y is C_1 - C_6 haloalkylene.

12. The compound of claim 10, wherein R^4 is C_3 - C_8 cycloalkyl.

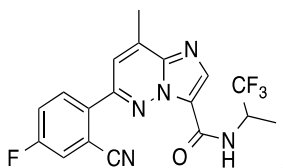
13. The compound of claim 11, wherein R^4 is C_1 - C_6 alkyl.

14. The compound of claim 1, wherein the compound is

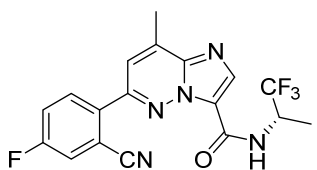


or a pharmaceutically acceptable salt thereof.

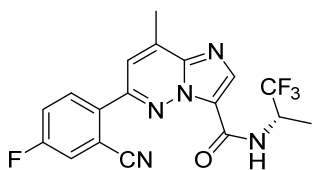
15. The compound of claim 14, wherein the compound is



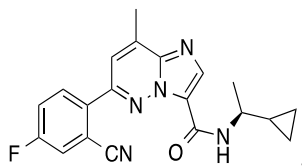
16. A compound having the following formula or a pharmaceutically acceptable salt thereof:



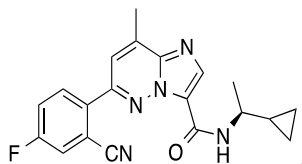
17. The compound of claim 16, wherein the compound is



18. A compound having the following formula or a pharmaceutically acceptable salt thereof:



19. The compound of claim 18, wherein the compound is



20. A pharmaceutical composition, comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

21. A pharmaceutical composition, comprising a compound of claim 7 and a pharmaceutically acceptable carrier.

22. A pharmaceutical composition, comprising a compound of claim 8 and a pharmaceutically acceptable carrier.

23. A pharmaceutical composition, comprising a compound of claim 9 and a pharmaceutically acceptable carrier.
24. A pharmaceutical composition, comprising a compound of claim 14 and a pharmaceutically acceptable carrier.
25. A pharmaceutical composition, comprising a compound of claim 15 and a pharmaceutically acceptable carrier.
26. A pharmaceutical composition, comprising a compound of claim 16 and a pharmaceutically acceptable carrier.
27. A pharmaceutical composition, comprising a compound of claim 17 and a pharmaceutically acceptable carrier.
28. A pharmaceutical composition, comprising a compound of claim 18 and a pharmaceutically acceptable carrier.
29. A pharmaceutical composition, comprising a compound of claim 19 and a pharmaceutically acceptable carrier.
30. A compound of claim 1 for use in treating a disorder selected from the group consisting of Gaucher disease, Parkinson's disease, Lewy body disease, dementia, multiple system atrophy, epilepsy, bipolar disorder, schizophrenia, an anxiety disorder, major depression, polycystic kidney disease, type 2 diabetes, open angle glaucoma, multiple sclerosis, endometriosis, and multiple myeloma.
31. Use of a compound of claim 1 in the manufacture of a medicament for treating a disorder selected from the group consisting of Gaucher disease, Parkinson's disease, Lewy body disease, dementia, multiple system atrophy, epilepsy, bipolar disorder, schizophrenia, an anxiety disorder, major depression, polycystic kidney disease, type 2 diabetes, open angle glaucoma, multiple sclerosis, endometriosis, and multiple myeloma.